CASE REPORT

Uncommon side effect with a commonly used targeted agent: sunitinib-induced nephrotic syndrome in a patient with metastatic renal cell carcinoma

Keith Ian Quintyne,¹ Triona Neenan,¹ Liam Casserly,² Rajnish Gupta¹

¹Department of Medical Oncology, University Hospital Limerick, Limerick, Ireland

²Department of Nephrology, University Hospital Limerick, Limerick, Ireland

Correspondence to
Dr Keith Ian Quintyne,
keithi.quintyne@hse.ie

Accepted 23 March 2014

SUMMARY

The authors report the case of a 67-year-old woman with metastatic renal cell carcinoma (RCC) without prior nephrectomy, who had received long-term exposure (38 months) to the oral multi-targeted tyrosine kinase inhibitor (TKI), sunitinib. She had a sustained clinical and radiological response to her therapy, but had this therapy discontinued due to the rare development of nephrotic syndrome.

BACKGROUND

Recently, the incidence of renal cell carcinoma (RCC) has been steadily rising and has been associated with an increase in cancer-specific mortality in Western Europe.¹ A potential contributing postulate given in the literature has been related to the previous significant lack of active systemic agents for use in the management of metastatic RCC.^{1 2}

However, with the advancement in the development of molecular-targeted therapies, tyrosine kinase inhibitors (TKIs) such as sunitinib have gained favour in the management of metastatic RCC. The pivotal work by Motzer *et al*³ in 2007 paved the way for the development of a systemic therapeutic option, when it was shown that the multi-targeted TKI sunitinib was associated with better quality of life and tolerability with an improved progression-free survival of 11 months and an objective response rate (ORR) of 31%, when compared with interferon α at 5 months and 6%, respectively.

There remains a paucity of data as to the optimal duration of therapy with TKI; but median duration exposure of 9–15 months is often stated.^{4–6} With longer exposure to targeted agents, there is an increased likelihood to develop cumulative or uncommon toxicities including the rarely seen side effects such as nephrotic syndrome which has a quoted incidence of less than 1%.^{7 8}

We report the case of a Caucasian woman of Irish extraction, who presented with metastatic RCC and tolerated an extended course of the oral TKI sunitinib for 38 months with minimal lasting toxicity, but subsequently developed severe nephrotic syndrome and had to permanently discontinue her therapy.

CASE PRESENTATION

A 67-year-old retired Irish teacher, without significant personal history namely alcohol or smoking

habits or family history of malignancy, who developed symptoms of unexplained fatigue, non-productive cough and worsening shortness of breath. Radiological evaluation with a plain chest radiograph revealed a right hilar mass, which warranted further investigation (figure 1). She underwent a bronchoscopy that revealed no endobronchial lesions. Biopsy of the hilar mass was obtained under radiological guidance and the histology and immunohistochemistry profile confirmed metastatic clear cell RCC (figure 2).

The thorax, abdomen and pelvic staging CT showed several right-sided pulmonary lesions, with the largest having a maximum diameter of 4 cm, and a 9 cm malignant appearing right kidney with no other evidence of systemic disease (figures 3 and 4).

Analysis of prognostic risk factors by the Heng criteria:⁶

- ▶ Corrected calcium level (Ca^{2+}): 2.30 mmol/L
- ▶ Haemoglobin (Hb): 11.5 g/dL
- ▶ Lactate dehydrogenase (LDH): 198 U/L
- ▶ Eastern cooperative oncology group (ECOG) performance status: 2 (Karnofsky performance status of <80%)
- ▶ Disease-free interval: less than 12 months.

In November 2009, she was assessed by the aforementioned criteria as being in intermediate risk, and was consequently started on sunitinib therapy at a dose of 50 mg/day on the schedule 4/2 (6-week cycles with 4 weeks on treatment and 2 weeks off treatment). She was able to achieve stable disease (SD) on serial radiological assessment

To cite: Quintyne KI, Neenan T, Casserly L, *et al*. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201183

Figure 1 Plain chest radiograph at presentation.

Figure 2 Specimen showing clear cell renal cell carcinoma on H&E staining.

for 38 months, with no new lesions developing while on therapy.

Toxicities reported for this patient in the first 6 months exposure to sunitinib included hypothyroidism (grade II), one episode of hand-foot syndrome (grade III), weight loss (>20% baseline weight) (grade III) and hypertension (grade III). These toxicities were managed through the initiation of thyroxine replacement, topical emollient therapy, reducing the sunitinib dose level to 37.5 mg/day (still on schedule 4/2) and introduction of hypertensive control with amlodipine. This allowed her to continue therapy without sustained side effects in an outpatient setting, with the almost complete regression of her presenting symptoms of a non-productive cough and shortness of breath.

In February 2013, she was allowed a drug holiday, as she had developed symptoms of worsening fatigue (grade III), weight loss (>20% baseline weight) (grade III) and peripheral leg oedema (grade II). Review of her serial biochemistry results noted a decline in her albumin levels and serial urinalysis has revealed increasing proteinuria warranting further evaluation (figure 5).

OUTCOME AND FOLLOW-UP

Sunitinib was discontinued permanently, and advice from the department of nephrology was sought with respect to the best

plan of integrated care for her, as her serum and urine biochemical indices were in keeping with a working diagnosis of nephrotic syndrome. Her other investigations including a lipid profile, viral serology and inflammatory markers were all unremarkable; however, a re-staging CT performed as part of her re-evaluation revealed evidence of local and distant progression of her underlying metastatic RCC. Given her declining ECOG performance status and deteriorating clinical picture, renal biopsy to confirm marked endothelial cell damage and rule out other potential causes was considered not to be appropriate.

Multidisciplinary review recommended starting her on corticosteroids in early March 2013, and has led to an improvement in her urinary indices, but her serum biochemistry remains relatively unchanged. These factors, coupled with her declining ECOG performance status prejudiced her from further therapy for her disease. The patient and her family were in agreement with this decision and she was subsequently admitted to a specialist palliative care facility for end-of-life care.

DISCUSSION

Advanced or metastatic RCC has been historically associated with a guarded prognosis,⁹ and as previously mentioned has been seen as an increasing cause of cancer-specific related mortality within the developed world.^{1 2} The main therapeutic option for many years that offered the best outcome was for patients to undergo cytoreductive surgery.^{1 10} Approximately 25% of patients with RCC will present with advanced or metastatic disease, which is not suitable for primary surgical intervention; and notwithstanding this, 33% who have undergone radical nephrectomy for early-stage disease have a risk of developing progressive disease, and may also eventually require some systemic option.^{2 10}

Historically, the main options for disseminated malignancy have been the use of chemotherapy or immunotherapy; however, with metastatic RCC this was associated with low response rates and high levels of side effects.^{9 11} RCC have been well known to be highly chemotherapy resistant with response rates of 4–6% being quoted in the literature.¹² The potential explanation for this observed poor ORR may be related to the expression of the multidrug resistance transporter in proximal-tubule cells, from which clear cell RCC originates.¹⁰ The other traditional choice was immunotherapy with interferon and

Figure 3 Staging CT of abdomen at presentation.

Figure 4 Staging CT of thorax at presentation.

Figure 5 Serial biochemical results.

interleukin, which had a median duration of response of as much as 6 months, but unfortunately did not significantly avert the course of the disease trajectory and most patients suffered with significant toxicities.⁹

Recently, the pharmacological arena has developed significantly with greater understanding of cancer biology and the necessary therapeutic pathways that can be targeted by TKIs. Multiple new agents including sunitinib have become available; this is an oral multi-target TKI that has both antitumour and antiangiogenic activity.^{1 13} It exerts its clinical effect by inhibiting phosphorylation of receptor tyrosine kinases (RTKs), through the inhibition of platelet-derived growth factor receptors (PDGF α and PDGF β), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 (FLT-3), colony-stimulating factor (CSF-1F) and the glial cell-line derived neurotrophic factor receptor (RET).¹⁴

Despite TKIs being designed to specifically target RTKs, it has become evident that TKIs may exert unexpected toxicity by initiating other cellular pathways. The incidence of toxicity may vary depending on several parameters including (1) patient's age, (2) patient's ECOG performance status, (3) associated medical comorbidities, (4) agent used, (5) dose and treatment schedule used, (6) concurrent medications used and (7) stage of disease.

The development of various side effects is due to TKIs' ability to interact with normal and tumour cells. More common side effects include (1) asthenia, (2) fatigue, (3) hair depigmentations, (4) cardiotoxicity, (5) hypothyroidism, (6) hypertension, (7) skin toxicity, (8) gastrointestinal disturbances and (9) haematological toxicities.¹ These are normally seen in more than 10% of patients who use sunitinib therapy.¹⁵

Sunitinib therapy may also be associated with the development of other less common toxicities.¹ These include (1) gastrointestinal perforation, (2) colonic pneumatosis, (3) rheumatoid arthritis, (4) encephalopathy syndrome, (5) chronic wounds and (6) hypophosphataemia.¹⁶ These may be seen in less than 1% of patients who use sunitinib therapy.¹⁵

The development of renal toxicity and proteinuria in patients undergoing antiangiogenic therapy, although rare, has been demonstrated during more prolonged exposure to sunitinib therapy.^{7 17} Reports have shown that approximately 0.1% of patients on sunitinib therapy may develop nephrotic syndrome (grade III/IV).¹⁵ The pathogenesis of this is likely to be related to the perturbation of the podocyte-endothelial vascular

endothelial growth factor (VEGF) axis signalling.¹⁸ VEGF is produced by podocytes, and VEGFR are present on normal glomerular capillary endothelial cells.¹⁹ Consequently, patients on antiangiogenic therapy (ie, anti-VEGF therapy) can ultimately develop proteinuria with nephrotic change and potentially impaired renal function,⁸ as demonstrated by our patient due to her long-term therapy with sunitinib.

This patient had tolerated her biological therapy with sunitinib reasonably well, as demonstrated by her long-term use. Although the standard initial dose was not maintained due to profound dermatological side effect experienced and she was not rechallenged at the full dose; interestingly in Motzer *et al*⁴ original paper, 50% of patients had to undergo dose modifications and were also never rechallenged. She developed an endocrinopathy from her RTK that was also seen by 14% of patients undergoing therapy with sunitinib.⁴ The most significant toxicity that compromised her global care was her nephrotoxicity, which presented after 38 months of therapy, well beyond her original expected overall survival of 20–24 months, has been reported in less than 1% of cases of patients on sunitinib, and is usually associated with renal impairment which was not demonstrated in this case.^{7 8}

Based on the Motzer *et al* data, sunitinib has now been incorporated into the treatment algorithms for patients with metastatic RCC, and hence provides a much required outpatient-based therapeutic option in the armamentarium for the treatment of patients with this disease.^{1 2}

Disease control becomes the ultimate goal as opposed to curative intent when managing patients with advanced disease; and these therapies that are undertaken should be able to maximise quality of life and have minimal toxicities. We are still very much in its infancy with respect to the use of targeted agents in the treatment pathway for patients and realising the benefits of outpatient therapy that is not plagued with the traditional toxicities seen with the use of cytotoxic therapy such as myelosuppression, nausea and vomiting and alopecia. However, with the expanding and extended use of these agents there will be increasing risks of encountering other side effects, and consequently greater vigilance is required to reduce complications for toxicities and the associated morbidity. Guidelines in this case did call for the regular monitoring of serum and urinary results and these became more profoundly worse even when the patient was on a drug holiday and should highlight the need for not being complacent in the review of all parameters in the evaluation process.

Learning points

- ▶ The patient had an excellent and extended stable disease on her biological therapy.
- ▶ Exceeded median overall survival for most patients with metastatic renal cell carcinoma.
- ▶ Highlights the fact that with prolonged use of these newer agents, there is a greater likelihood of developing severe and rare toxicities such as nephrotic syndrome.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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